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Review Paper

The Role of APC in Wnt/ β-Catenin Pathway in Gastric Cancer

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ABSTRACT

Most of signaling pathways play a basic role in controlling of embryonic development and cell proliferation in adult tissues. In recent years, mutations that affected on components in most of these pathways have been linked to a type of human cancer. For example, APC (adenomatosis polyposis coli) is the first of critical gene that mutated in the development of colon cancer, as part of the Wnt signaling pathway is known. Cancer development associated with genetic and epigenetic modifications. Studies show that APC including genes that involved through these modifications in cancer, such as gastric cancer. APC is a tumor suppressor protein that regulates part of the Wnt signaling pathway. The protein binds to I²-Catenin, Axin (a scaffold protein) and Gsk3 (glycogen synthase kinase 3) in the cytoplasm and promoted I²-Catenin phosphorylation via Gsk3. phosphorylated I²-Catenin destroyed by the proteasome and thereby inhibits Wnt signaling pathway. On the other hand APC has a nuclear localization signal (NLS) and nuclear export signal (NES). If in the presence of Wnt signal, accumulates I²-Catenin in cytoplasm enters into nucleus, APC connected to accumulated I²-Catenin in nucleus through binding domains and with its shuttling activity translocated I²-Catenin between nucleus and cytoplasm; therefore regulated level and transcriptional activity of I²-catenin in nucleus. If binding region to I²-Catenin of APC genes is mutated, does not occur Wnt signaling inhibition and caused uncontrolled proliferation of cells that lead to cancer cells. In general APC downregulated Wnt signaling pathway and caused cell proliferation inhibition, which indicates the important role of this protein as a tumor suppressor. In addition, APC is one of the genes that are commonly in gastric cancer hypermethylated and APC promoter hypermethylated helps activation of Wnt middle that is associated with development of gastric adenoma. Above shows that the APC as a tumor suppressor plays an important role in Wnt/I²_Catenin signaling pathway. Mutations in this gene can cause gastric cancer, but removing this gene did not influence in incidence of gastric cancer also involved in the development its.

Keywords: APC, Wnt Signaling, I²-Catenin, Gastric Cancer, Tumor-suppressor.

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Most of signaling pathways play a basic role in controlling of embryonic development and cell proliferation in adult tissues. In recent years, mutations that affected on components in most of these pathways have been linked to some specific type of human cancer. For example, APC (adenomatosis polyposis coli) is the first critical gene that mutated in the development of colon cancer, as part of the Wnt signaling pathway that was known very good. This protein initially identified as a responsible element of familial adenomatous polyposis (FAP) (1, 2). APC is a multi-functional tumor suppressor protein that partially regulates Wnt signaling pathway.

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APC is a multi-functional tumor suppressor protein that partially regulates Wnt signaling pathway. APC gene has an 8538-base-pair open reading frame and 15 exons that produces a 312-kDa protein composed of 2843 amino acids and it seems that APC greatly expressed during embryonic and postnatal periods in a variety of tissues, including brain and the gastrointestinal tract (3, 4).

APC is a large protein with multiple domains that binds to the variety of proteins. These domains include oligomerization domain and armadillo domain in the N-terminus, ,a series of 15- and 20-amino-acid repeats in the central portion, and a basic domain and binding sites for EB1 and the mammalian homologue of discs large (DLG) at the C-terminus (see Fig.1). By these multiple domains, APC binds to numerous proteins, this property allows APC to accomplish functions in not only tumor suppression but also cell differentiation, adhesion, polarity formation, migration, development, apoptosis, and neuronal functions. So, APC performs many cellular functions through these connection subunit (5, 6).

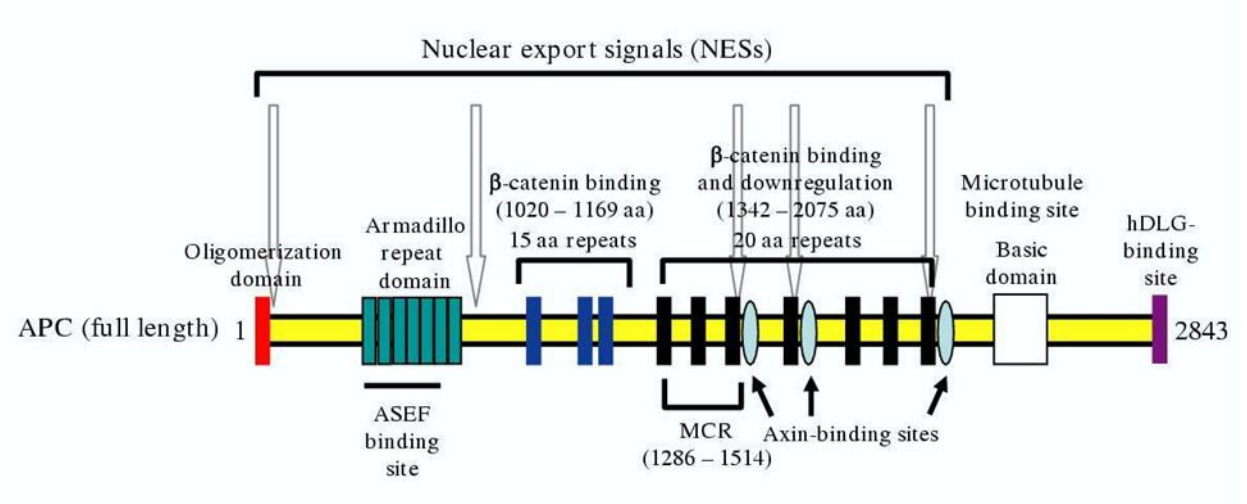

Fig. 1. The structure of the human adenomatous polyposis coli (APC) protein. APC contains multiple domains (7).

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β-Catenin was identified as the first binding protein to APC (8). β-Catenin is an adherent junction protein associated with the epithelial cell–cell adhesion protein E-cadherin. This discovery was a breakthrough that founded a relationship between human colon cancer and epithelial cell adhesion (9). Recent studies showed that APC protein is relevant to α-and β-catenin and the microtubule cytoskeleton, this indicates that the APC implicated in cell adhesion and morphological phenotype (10).

The protein binds to β-Catenin, Axin (a scaffold protein) and Gsk3 (glycogen synthase kinase 3) in the cytoplasm and promoted β-Catenin phosphorylation via Gsk3 (11). Phosphorylated β-Catenin destroyed by the proteasome and thereby inhibits Wnt signaling pathway; which is the most important role of APC as a tumor suppressor protein (12) (fig.2).

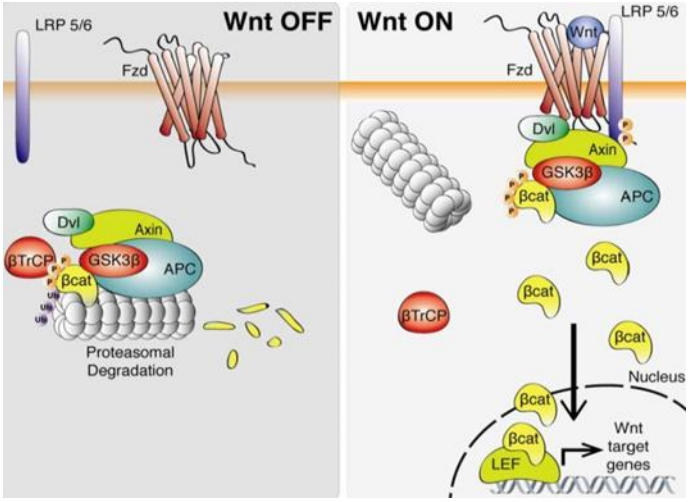

Fig.2. Wnt signaling pathway. In the absence of Wnt signal, complex consisting of 4 protein: APC (as a tumor-suppressor), Axin (a scaffold protein), Gsk3 (glycogen synthase kinase 3) is phosphorylated and subsequently phosphorylated β-catenin is then ubiquitinated and degraded in proteasomes. In the presence of Wnt, be prevented of complex formation, in result accumulated β-catenin in the cytoplasm and transported to the nucleus; accumulated β-catenin in the nucleus increased the activity of transcriptional activity of TCF/LEF (factorT_cell/lymphoid_enhancing factor connectivity) (13).

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Cytosolic over expression of β-catenin and its nuclear translocation is a common feature in screening of intestinal-type stomach cancer. It has been demonstrated that mutations in the APC and third exon of β-catenin caused to reduce of β-Catenin phosphorylation and prevent the destruction of this protein (14, 15). On the other hand APC has a nuclear localization signal (NLS) and nuclear export signal (NES). If in the presence of Wnt signal, accumulates β-Catenin in cytoplasm enters into nucleus, APC connected to accumulated β-Catenin in nucleus through binding domains and with its shuttling activity translocated β-Catenin between nucleus and cytoplasm; therefore regulate level and transcriptional activity of β-catenin in nucleus (16).

For this purpose the APC central protein contains three 15-amino-acid repeats and seven 20-amino-acid repeats can provide suitable binding sites for β-catenin (17). The binding of β-catenin to the 15-amino-acid repeats alone does not cause to the down regulation of β-catenin, but for down regulation its require at least 3 of the seven 20-amino-acid repeats (18).

If binding region to β-Catenin of APC genes is mutated, Wnt signaling inhibition does not occur and caused uncontrolled proliferation of cells that lead to cancer cells. In addition, APC is one of the genes that are hypermethylated commonly in gastric cancer and APC promoter hypermethylation helps activation of Wnt middle that is associated with development of gastric adenoma (19, 20).

APC also binds directly to DNA molecule. APC has three DNA-binding domains and all the domains contain the tandem repetitive S/TPXX sequences. These information indicates that APC binds preferentially to A/T-rich DNA sequences and regulates transcription (21).

The most mutations of APC result in truncation of the gene products, both of the germinal and somatic mutations of APC, through nonsense or frame-shift mutations causing the truncation of APC gene products. These truncated APC proteins can be nonfunctional, and in the case of activation may bind to wild-type APC protein and inactivate them. Identify truncated APC proteins can be used as an identification method of APC mutations (5).

Clinical studies have shown that deletion or mutation in the APC gene described above was seen in one third of cases with gastric cancer. Also it was shown that APC mutations is common in cases of intestinal-type gastric cancer more than other types of gastric cancer. As well as one series of gastric cancer patients showed a 33% frequency of mutated in colon cancer (MCC) mutations (13).

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Also investigations showed that somatic mutations identified in 25% of malignant gastric adenomas (22) and deletion of APC gene was found in 20-60% of cases of gastric cancer (23).

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Conclusion

This review set out to show that the APC as a tumor suppressor plays an important role in Wnt/β_Catenin signaling pathway. In addition, studies have shown that although mutations in the APC protein can involve in creating of gastric cancer, but removing this gene did not influence in incidence of gastric cancer also involved in the development it (24).